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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,379	12/09/2003	Daniel Zamanillo Castanedo	P03,0588 (29478-0015)	4441

26574 7590 01/19/2010

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
01/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,379	CASTANEDO ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,9,17-21,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 9, 17-21, 28, and 29,* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 09/11/2009 in response to office action mailed on 05/11/2009 has been acknowledged.

Claim 1 is amended.

Claim 3, 6, 8, 14-16 are canceled

Claims 1, 5, 9, 17-21, 28, and 29, *are pending and are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Withdrawn: Double patenting rejections for the reasons of record as set forth in the office action mailed on 05/11/2009 is withdrawn in view of Applicants cancellation of duplicate claims.

Withdrawn: Claims 1-3, 5-6, 8, 17-19 and 22-28 rejection under 35 U.S.C. 112, first paragraph (enablement) for the reasons of record as set forth in the office action mailed on 05/11/2009 is withdrawn in view of Applicants amendments and in view of a revised rejection below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1, 5, 9, 17-21, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a germ line transgenic mouse whose germ cells and somatic cells are homozygous for a targeted disruption in the endogenous gene encoding the Sigma-1 receptor protein wherein said gene disruption is obtained by a homologous recombination event with the vector identified as pHR53TK that is deposited in the CECT under the accession number CECT 5737 and

wherein said transgenic mouse and the cells isolated from said transgenic mouse completely lack a detectable level of expression of the endogenous sigma-1 receptor, does not enable a transgenic mouse with any mutation in said endogenous sigma-1 receptor gene and does not enable a cell from said mouse that is hetrozygous. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As claimed the base claim 1 includes a phrase “comprises a mutation" on line 2 that in its breadth encompasses any mutation. Any mutation will not do for completely inactivating sigma-1 receptor activity. Further, the specific targeting vector used for gene disruption could only cause a knockout disruption of the gene in a defined way. Further any cell that is heterozygous for disruption is not enabled for a use as it still expresses the functional sigma receptor and behaves like wild type cell. Still further any offspring of said mouse is not enabled as the nature of the offspring depends on the genotype of the mating partner. Only enabled are a fraction of its offspring that predictably possess said homozygous gene disruption. Any transgene or any positive selection marker in the disrupted gene will not do because the Applicant indicates in the base claim of using a specific vector (pHR53TK that is deposited in the CECT under the accession number CECT 5737) as defined and the specification discloses a single and specific gene or a positive selection marker in said vector. The applicant’s disclosure thus does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation. At issue, under the enablement requirement of 35 U.S.C.112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. “Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Response to Applicants arguments of 09/11/2009:

The Applicant amends the base claim and argues that with the amendments the claims over come 35USC112 1stparagraph enablement rejection.

The Applicants arguments are however found not persuasive because as indicated in the rejection the base claim 1 includes a phrase “comprises a mutation" on line 2 that in its breadth encompasses any mutation. Any mutation will not do for completely inactivating sigma-1 receptor activity. Further, the specific targeting vector used for gene disruption could only cause a knockout disruption of the gene in a defined way. Further any cell that is heterozygous for disruption is not enabled for a use as it still expresses the functional sigma receptor and behaves like wild type cell. Still further any offspring of said mouse is not enabled as the nature of the offspring depends on the genotype of the mating partner. Only enabled are a fraction of its offspring that predictably possess said homozygous gene disruption. Any transgene or any positive selection marker in the disrupted gene will not do because the Applicant indicates in the base claim of using a specific vector (pHR53TK that is deposited in the CECT under the accession number CECT 5737) as defined and the specification discloses a single and specific gene or a positive selection marker in said vector. Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 21, and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (U.S. Pat. No.5, 464,764; art of record) in view of Seth et al., (2000, Biochemical and Biophysical Research communications 241: 535-540; art of record).

The claims are directed to a process of making a mutant mouse that is homozygous for a disruption in an endogenous Sigma receptor gene using a gene targeting vector.

Capecchi teaches a vector to be used to produce knockout (gene disrupted) mouse. In particular Capechi teaches that a targeting vector has a first and a second segments of homologous DNA sequence, and a positive selection marker between the two homologous sequences. See Figure 1. Furthermore, they teach various markers that can be used in these vectors (Table 1. col.7-8). They teach that these vectors can then be used to produce transgenic animals, wherein ES cells are the target cells (Col. 15, lines 59-67), wherein the vector can then be introduced into the ES cells by electroporation or microinjection. These transformed ES cells can then be combined with a blastocysts and then grown and contribute to the germ line of the resulting chimeric animal (Col. 16, lines 1-10). They teach that cell lines from the animals can then be used to characterize gene function, or be used in assays (Col. 12-13, bridging paragraph). Capecchi clearly show that these vectors and methods can be used to determine the biological function of any known gene of interest. Capecchi however, does not teach the sequence for Sigma receptor gene.

Seth teaches that cDNA sequence of Sigma I receptor (Abstract, p.536), a known sequence that would fulfill the limitations of the claims, because this sequence would be considered homologous to at least a portion of the endogenous Sigma receptor gene (p.538 and Figure 2).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homologous sequences in targeting vectors as taught by Capecchi with segments of DNA sequence for Sigma I receptor by isolating and using the genomic segments for the Sigma-1 receptor cDNA taught by Seth and to make a targeting construct and use said construct to generate a gene disrupted mouse, and further breed them to generate a homozygous gene disrupted mouse where the genome of the mouse comprises a homozygous disruption of a Sigma receptor I gene where in said mouse lacks detectable level of said receptor. One would have been motivated use the method making a targeting vector and for producing mice having a

homozygous disruption of sigma receptor gene as they may provide a disease model for investigating the art described diseases or conditions associated with sigma receptors malfunctions. One would have a reasonable expectation of success of making and using Sigma receptor gene disrupted mouse as prior art fully provides the requisite teaching, suggestion and motivation to make and use said gene disrupted mouse. Thus, the claimed invention was *prima facie* obvious.

Response to Applicants arguments of 09/11/2009:

The Applicant amends the base claim and argues that with the amendments the claims overcome the obviousness of the invention 35USC103 rejections of record as set forth in the office action mailed on 05/11/2009. in particular the Applicant argues that making a gene targeting vector and the method of gene targeting as espoused by Capecchi and Seth references.

The Applicants arguments are however, found not persuasive because the Applicants gene targeting vector construction as well as the method of gene targeting strictly follows the patented method of Capecchi. Thus substituting the first and second gene segments of gene to be targeted as taught in Capecchi with the established segments of Sigma-1 receptor as taught by Seth in Capecchi's vector is clearly following a well established protocol of the prior art. Further the method of using said gene targeting vector for targeting an endogenous gene, screening for the positive ES cell clone, and breeding for a positively targeted mouse completely follows well established prior art protocol of Capecchi. Hence the method or the process of making instant Sigma-1 receptor mouse as described in the Application are again clearly obvious to one of skill in the art. The only aspect of the this method that is not obvious a priori is the end product, i.e., the nature of transgenic mouse generated. The gene disruption could be embryonic lethal, it could be lethal at different steps of early or late development. If not developmentally lethal, the adult targeted mouse may possess an expected overt phenotype or a no-overt phenotype etc. The transgenic animal so obtained is patentable, if it could be shown, that the transgenic animal so obtained is of credible, specific and/or of substantial utility or of a well established utility. The

Applicant further should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). Since the method followed for making the vector construct and method followed in targeting to obtain a gene disrupted mouse of the instant invention is well established in the prior art the invention as instantly claimed is clearly obvious to that extent. Hence the rejection is maintained.

Conclusion:

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at

(571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/
Primary Examiner, Art Unit 1633